Vol. 97 (2003) (SUPPLEMENT B), S21–S26
respiratoryMEDICINE

Comparison of the efficacy and safety of high doses of beclometasone dipropionate suspension for nebulization and beclometasone dipropionate via a metered-dose inhaler in steroid-dependent adults with moderate to severe asthma

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Abstract Nebulization for the administration of high doses of inhaled corticosteroids can benefit steroid-dependent asthmatics. The objective of this double-blind, double-dummy, multicentre, randomized, parallel-group study was to compare the efficacy and safety of high-dose corticosteroids given by nebulization or metered-dose inhalation in adult patients with asthma. Following a 2-week run-in period, 124 patients, aged 18–70 years, with moderate to severe asthma treated with high-dose inhaled steroids were randomized to one of two treatment groups for 12 weeks: beclometasone dipropionate (BDP) suspension for nebulization 3000–4000 μg day^{-1} b.i.d. given via a nebulizer (n=63), or BDP spray 1500–2000 μg day^{-1} b.i.d. given via a metered-dose inhaler (MDI) plus spacer (BDP MDI) (n=61). Comparable improvements over baseline, which were statistically significant in most cases, were reported at study end for the two treatment groups in the various efficacy parameters evaluated (pulmonary function tests, clinical symptoms scores, and the use of rescue salbutamol). The primary efficacy endpoint was morning pulmonary expiratory flow rate (PEFR). For the intent-to-treat population, in the BDP nebulization group mean morning PEFR increased statistically significantly from 308.7 ± 107.8 l min^{-1} to 319.2 ± 104.0 l min^{-1}, while in the BDP MDI group the increase was from 301.5 ± 94.7 l min^{-1} to 309.3 ± 86.7 l min^{-1}. The two treatments were equally well tolerated. A total of 19 patients in each group reported adverse events during the treatment period, and these were generally mild–moderate in severity. In conclusion, the results of this study demonstrate that BDP suspension for nebulization 3000–4000 μg day^{-1} given via a nebulizer and BDP spray 1500–2000 μg day^{-1} given via an MDI plus spacer are equally effective, with an acceptable safety and tolerability profile, when used in steroid-dependent adult patients with moderate to severe asthma.

Keywords asthma; beclometasone dipropionate; inhaled drugs; metered-dose inhaler; nebulized drugs.

INTRODUCTION

Nebulization for the administration of high-dose inhaled corticosteroids is recommended for asthmatic patients who are dependent on steroid therapy and also need cycles of oral steroids (1). This mode of therapy facilitates the administration of high doses of the drugs, which may be delivered simultaneously to the upper and lower respiratory tract (2). In addition, nebulization therapy for corticosteroids has been reported to allow for a reduction in the dosage of oral steroids in severe asthmatic adults (3).

The purpose of this study was to compare the efficacy and safety of a high dose of a new formulation of beclometasone dipropionate (BDP) suspension for nebulization administered via a nebulizer and high-dose BDP spray administered via a metered-dose inhaler (MDI) plus spacer (BDP MDI) in steroid-dependent adults with moderate to severe asthma.

MATERIALS AND METHODS

Male and female outpatients, aged ≥ 18 to ≤ 70 years, with a clinical diagnosis of moderate to severe asthma [as defined by the National Heart, Lung and Blood Institute (4)], undergoing treatment with high-dose inhaled steroids at a constant daily dosage in the previous 4 weeks, with predicted forced expiratory volume in 1 second (FEV_1) of ≤ 60% prior to use of the inhaled

steroids, with stability of lung function as indicated by peak expiratory flow rate (PEFR), and with a positive response to the reversibility test (defined as an increase of at least 10% in FEV_1 measured 30 min following two puffs (2 × 100 μg) of inhaled salbutamol MDI) were eligible to participate in the study. Patients with evidence of asthma exacerbation or symptomatic infection of the airways in the previous 4 weeks, with the likelihood of exposure during the study to allergens or occupational sensitizing agents of a seasonal or episodic nature proven or suspected to affect the patients, with a history of clinically significant cardiac, renal, neurological, hepatic, or endocrine disease, treated with oral steroids in the previous 8 weeks, hypersensitive to inhaled corticosteroids, involved in another trial, and with ≥ +15% variation in FEV_1 from start to end of the study run-in period were excluded from the randomization.

Study design

This was a 14-week, double-blind, double-dummy, randomized study undertaken in two parallel groups at nine centres. Following a 2-week run-in period in which patients continued treatment with the inhaled steroid that they were previously using, patients who met study entry criteria were assigned by randomization to one of the two treatment groups for a treatment period of 12 weeks using a daily dosage equivalent to that of the previously inhaled steroid: BDP suspension for nebulization 3000–4000 μg day^{-1} b.i.d. (Clenil-A®, Chiesi Farmaceutici SpA, Italy), plus three to four puffs twice-daily of placebo spray, or BDP spray 1500–2000 μg day^{-1} b.i.d. (three to four puffs twice-daily) (Becloforte®, Allen & Hanburys, U.K.), plus placebo suspension for nebulization twice-daily. The suspension for nebulization was administered using a Pari Boy® compressor and an LC Plus® nebulizer (Pari Turbo Boy®) (Pari, Germany), and the spray was given via an MDI plus spacer (Volumatic®, Allen & Hanburys, U.K.). Inhaled (other than the test BDP and the permitted inhaled steroids) or oral corticosteroids, oral or long-acting inhaled bronchodilators, antihistamines other than for rhinitis, anticholinergics, and leukotriene antagonists were excluded. The use of inhaled steroids during the study run-in period only at the same daily dosage used during the previous 4 weeks, inhaled salbutamol (Ventolin®, Glaxo-Wellcome, U.K.) given via an MDI, inhaled or oral sodium cromoglycate or nedocromil sodium, or theophyllines, in patients already receiving these and used at a constant daily dosage during the study period, antihistamines as rescue medication for rhinitis, and appropriate treatment for concomitant disease if it did not interfere with study evaluation parameters was permitted. Patients were assessed at various clinic visits during the study: at the start of the run-in period, at the start of active treatment, and at 2-week intervals post-randomization.

Lung function measurements were conducted according to the Official Statement of the European Respiratory Society (5) in the morning at approximately the same hour of the day. Spirometric lung function parameters were measured at each clinic visit. Morning and evening PEFRs were measured daily by patients using the Mini-Wright® peak flow meter (Markos, Italy/Clement Clarke International, U.K.) and the highest of three measurements recorded on a diary card. Clinical symptoms scores, rated on a four-point scale (from 0=no symptoms to 3=severe symptoms), and salbutamol consumption, were also assessed daily by patients and recorded on a diary card. Patient opinion of efficacy, and investigator opinion of tolerability based on adverse drug reactions, were rated on a four-point scale ranging from 'poor' to 'excellent' and recorded at study end. Morning serum cortisol levels were measured at the start and end of randomization, and vital signs at each clinic visit. The institutional review board for each treatment centre approved the protocol, and written informed consent was obtained from the patients.

Assessments

The primary efficacy endpoint was morning PEFR. Secondary efficacy variables were evening PEFR, FEV_1, forced vital capacity (FVC), daily salbutamol consumption, clinical symptoms scores, and patient opinion of efficacy. The primary safety parameter was the morning serum cortisol level. Secondary safety variables included adverse events and adverse drug reactions, vital signs (heart rate and blood pressure), and investigator opinion of tolerability.

Statistical analysis

Sample size calculation (6) was based on the criteria of equivalent efficacy between the two treatments. Considering as the primary efficacy variable the final mean value of morning PEFR, the following was taken into account: the baseline-adjusted final mean value obtained in the BDP MDI group was estimated to equal 460 l min^{-1}; the equivalence of efficacy between groups was defined as a difference between mean values not more than 10% of the BDP MDI mean; the standard deviation of the difference between mean values was estimated as equal to 70 l min^{-1}; the expected difference between the mean value in the two groups was estimated as equal to 0; the power of the trial was defined as equal to 80% and the level of significance equal to 5%.

Statistical significance in the study was declared if $P \leq 0{\cdot}05$. Baseline values were compared using an ANOVA (analysis of variance) model (including a term for treatment effect) for continuous variables, and by the Wilcoxon two-sample test or Chi-square test for categorical variables.

Table 1. Baseline demographic and lung function data for the randomized population of steroid-dependent adults with moderate to severe asthma treated with BDP suspension for nebulization or BDP via metered-dose inhaler

Demographic characteristics/ lung function parameters	Beclometasone dipropionate via a nebulizer	Beclometasone dipropionate via a metered-dose inhaler
Gender		
Male	29	31
Female	34	30
Total	63	61
Mean ± SD age (years)	45·2 ± 12·2	47·3 ± 12·8
Mean weight (kg)	72·9	75·6
Mean height (cm)	168·7	167·2
Mean ± SD morning PEFR ($l\ min^{-1}$)	308·7 ± 107·8	301·5 ± 94·7
Mean ± SD evening PEFR ($l\ min^{-1}$)	320·1 ± 108·3	313·5 ± 96·8
Mean ± SD FEV_1 (l)	1·8 ± 0·7	1·9 ± 0·6
Mean ± SD FVC (l)	2·6 ± 0·8	2·8 ± 0·8

PEFR, peak expiratory flow rate; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

Within-treatment comparisons for morning PEFR were analysed by calculating the 95% confidence interval for the mean change from baseline, and between-treatment comparisons by using the analysis of covariance (ANCOVA) model for values at each study visit. This model included terms for investigator and treatment effects and baseline value as a covariate. A preliminary test for the investigator-by-treatment interaction was undertaken at 0·10 significance level. Therapeutic equivalence between the two treatments was evaluated by calculating the 95% confidence intervals for the difference between the least square means (LSM), from ANCOVA, in the two groups. The two test treatments were defined to be equivalent if the confidence limits for the difference fell within ±10% of the least square-adjusted mean of the BDP MDI group. Furthermore, BDP nebulization was defined as non-inferior to BDP MDI if the lower limit of the unilateral confidence interval for the difference in morning PEFR did not exceed −10%.

Secondary efficacy parameters were analysed by calculating the 95% confidence interval for the mean change from baseline at each visit (for variables measured at clinic visits) or at each 2-week period (for values recorded by patients), and within- and between-treatment comparisons were undertaken using ANCOVA. Patient opinion of efficacy was compared using the Chi-square test.

Morning cortisol serum levels and cardiovascular parameters were analysed by calculating the 95% confidence intervals for the changes from baseline. Between-treatment comparisons for cortisol levels were made using the unpaired *t* test, for the incidence of adverse events, and adverse drug reactions, using the Chi-square test or the two-tailed Fisher's exact test, and for investigator opinion of tolerability using the Chi-square test.

All randomized patients who received at least one dose of the study medications and with at least one visit after baseline were included in the intent-to-treat (ITT) analysis. Missing data were replaced with the LOCF (last observation carried forward) method. All patients included in the ITT analysis who also met study entry criteria and did not have any major protocol violations were included in the per protocol (PP) analysis. The primary efficacy variable was analysed both for the ITT and PP populations, while all other efficacy parameters were analysed on an ITT basis only.

RESULTS

Patient population

Of the 135 patients screened for the study, 124 patients were randomized: 63 to the BDP nebulization group, and 61 to the BDP MDI group. Nine patients (four in the BDP nebulization group and five in the BDP MDI group) were withdrawn during the active treatment period due to various reasons, and 12 patients (six in each treatment group) were excluded from the PP population due to major protocol violations. The ITT population was therefore made up of 124 patients (63 treated with BDP nebulization and 61 treated with BDP MDI), and the PP population of 112 patients (57 treated with BDP nebulization and 55 treated with BDP MDI). Assessment of safety of the two treatments was based on the ITT population. Patient demography and values for lung function parameters at baseline were comparable for the two groups in the randomized population (Table 1).

Evaluation of efficacy: Morning PEFR

Comparable and statistically significant improvements in morning PEFR were reported over baseline in both the

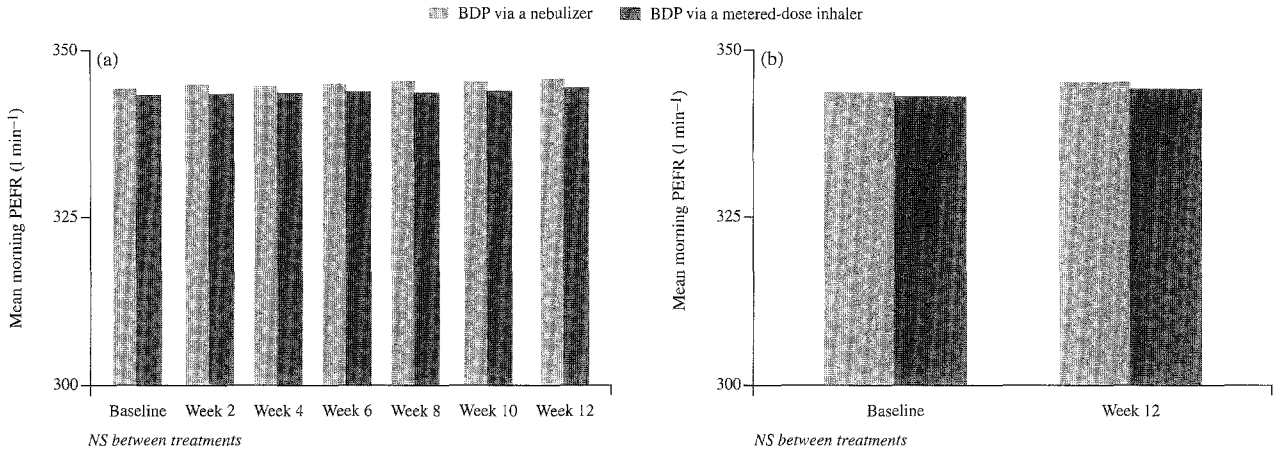

FIGURE 1. Mean values for morning peak expiratory flow rate in the (a) intent-to-treat and (b) per protocol populations of steroid-dependent adults with moderate to severe asthma at baseline and during 12 weeks of treatment with beclometasone dipropionate given by nebulization or metered-dose-inhalation.

BDP nebulization and BDP MDI groups in the ITT population at the end of the 12-week treatment period. In the BDP nebulization group, mean values increased from 308·7 l min^{-1} to 319·2 l min^{-1}, while in the BDP MDI group the increase was from 301·5 l min^{-1} to 309·3 l min^{-1} (Figure 1). Similar results were also seen in the PP analysis, with mean values increasing from 305·1 l min^{-1} at baseline to 315·4 l min^{-1} at treatment end in the BDP nebulization group, and from 299·6 l min^{-1} to 307·6 l min^{-1} in the BDP MDI group (Figure 1). Furthermore, the lower limit of the unilateral confidence interval was –7·4 and –8·4 in the ITT and PP populations, respectively, and did not exceed –10% (–31·4 and –31·1, respectively) of the adjusted mean of the BDP MDI group, thus demonstrating that BDP nebulization was not inferior to BDP MDI. In addition, the 95% bilateral confidence intervals for the difference between the LSM in the ANCOVA model were –9·6; 17·3 for the ITT population, and –11·0; 18·3 for the PP population, and fell within ±10% of the adjusted mean of the BDP MDI group (±31·4 l min^{-1} and ±31·1 l min^{-1}, respectively), to confirm that the two treatments were equivalent.

Evaluation of efficacy: Other measures of pulmonary function

Statistically significant improvements were seen over baseline in both groups in the ITT population at treatment end in evening PEFR, FEV_1, and FVC, with no significant differences found between the two treatment arms for any of these parameters (Figure 2). Mean values for the BDP nebulization and BDP MDI groups, respectively, increased from 320·1 l min^{-1} to 333·8 l min^{-1} and from 313·5 l min^{-1} to 326·6 l min^{-1} for evening PEFR, from 1·8 to 2·2 litres and from 1·9 to 2·2 litres for FEV_1, and from 2·6 to 3·0 litres and from 2·8 to 3·0 litres for FVC.

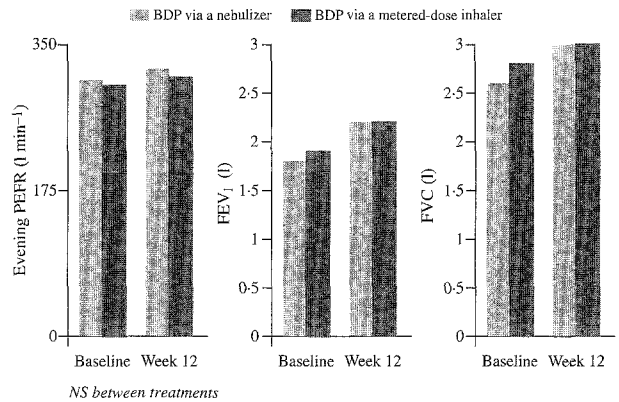

FIGURE 2. Mean values for various lung function parameters in the intent-to-treat population of steroid-dependent adults with moderate to severe asthma before and after 12 weeks of treatment with beclometasone dipropionate given by nebulization or metered-dose-inhalation.

Evaluation of efficacy: Signs and symptoms and rescue medication

At study end, similar and statistically significant reductions in the sum of clinical symptoms scores were observed over baseline in the two treatment groups when analysed on an ITT basis. Scores fell from 4·3 to 3·2 in BDP nebulization-treated patients, and from 4·6 to 3·4 in the BDP MDI group.

Reductions in the daily consumption of salbutamol were also noted in both treatment arms at the end of the study when compared with baseline, these being statistically significant in the BDP nebulization group at the end of the test treatment period, and in the BDP MDI group at 2 weeks post-treatment. At study end, the difference between the two groups was non-significant, with the mean daily number of puffs falling from

Table 2. Adverse events reported in steroid-dependent adults with moderate to severe asthma during 12 weeks of treatment with beclometasone dipropionate suspension given by nebulization or metered-dose-inhalation

Parameter	Beclometasone dipropionate via a nebulizer (n=63)	Beclometasone dipropionate via a metered-dose inhaler (n=61)
Number of patients with adverse events	19 (30·2%)	19 (31·1%)
Number of adverse events	29 (46%)	31 (50·8%)
Number of patients with treatment-related adverse events	6 (9·5%)	5 (8·2%)
Number of treatment-related adverse events	13 (20·6%)	7 (11·5%)
Number of dropouts due to treatment-related adverse events	1	1

3·8 puffs day^{-1} at baseline to 3·3 puffs day^{-1} in the BDP nebulization group, and from 3·7 puffs day^{-1} to 3·4 puffs day^{-1} in the BDP MDI group.

Evaluation of efficacy: Patient opinion

The majority of patients in both treatment groups in the ITT population considered efficacy as 'excellent' or 'good' (83% and 82·2% of patients in the BDP nebulization and BDP MDI groups, respectively), with no significant difference noted between the two treatment arms.

Evaluation of safety

Safety data showed that both treatments were well tolerated. During the treatment period, 19 patients in each group (30·2% and 31·1% of BDP nebulization-treated and BDP MDI-treated patients, respectively) reported adverse events (NS between treatments) (Table 2). The respective number of adverse events was 29 (46%) and 31 (50·8%), and these tended to be mild to moderate in severity and were generally associated with the respiratory system. In total, 11 patients reported adverse drug reactions: six (9·5%) in the BDP nebulization group, and five (8·2%) in the BDP MDI group, with 13 (20·6%) and 7 (11·5%) adverse drug reactions seen in the respective groups. Adverse drug reactions generally consisted of local irritation or infection/inflammation. Only two patients (one in each group) were withdrawn from the study due to adverse events.

The two treatments had a similar effect with respect to morning serum cortisol levels at treatment end, and no clinically or statistically relevant changes were found for vital signs within or between groups during the treatment period. Furthermore, investigator opinion of tolerability was 'excellent' or 'good' in 96·6% and 94·6% of patients in the BDP nebulization and BDP MDI groups, respectively (NS between treatments).

DISCUSSION

This study was designed to evaluate the efficacy and safety of a high dose of a new formulation of BDP suspension for nebulization given via a nebulizer and high-dose BDP spray given using an MDI plus spacer as a 12-week treatment for moderate–severe asthma in adult patients dependent on high-dose inhaled steroids.

Although no previous studies have compared BDP delivered via nebulizer and MDI, many studies in adults involving bronchodilators have compared these two delivery devices. A recent review by Brocklebank *et al.* described a combined analysis of 21 studies in adult stable asthma (7). They found equivalence for the main pulmonary outcomes and no evidence of difference in other outcomes. In summary, the authors concluded that the dosage equivalence ratio of MDI to nebulizer is 1:2–1:6.

The results of this study demonstrated that nebulized and MDI forms of BDP significantly, and to a similar degree, improved pulmonary function and asthma symptoms, and reduced the need for rescue medication. The majority of patients in both groups also considered efficacy to be 'good' or 'excellent'. Furthermore, statistical analysis of the results for the primary efficacy variable of morning PEFR confirmed that BDP nebulization was not inferior to BDP MDI and that the two treatments were equivalent. When considering that the daily dosage of the two treatments was equivalent to that of the previous treatment with inhaled corticosteroids, it is noteworthy that there was still scope for improvement for the efficacy parameters evaluated, as demonstrated by the differences over baseline in both groups. This can be explained by the good compliance (the administration of at least 75% of the scheduled doses), of around 90%, with the two treatments. It is also important to note that compliance was evaluated using a very restrictive method that required the use of the minimum necessary doses of the active drugs and the alternative placebo. In addition, the safety profile was shown to be comparable for the two treatments with respect to the incidence of adverse events, potential adrenal suppression (as indicated by morning serum cortisol levels), and vital signs.

In conclusion, this study demonstrates that BDP suspension for nebulization 3000–4000 μg day^{-1} given via a nebulizer and BDP spray 1500–2000 μg day^{-1} given via

an MDI plus spacer are effective and therapeutically equivalent, with a good safety and tolerability profile, when used as a treatment for moderate to severe asthma in steroid-dependent adult patients.

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